What is claimed is:

1. A method for production of virus or viral antigen, comprising the steps of (a) providing a culture of adherent cells bound to a microcarrier, (b) growing the cell culture to confluence, (c) infecting the cells with a virus and (d) incubating said culture of cells infected with said virus to propagate said virus, wherein the cell density of the biomass of the cell culture grown to confluence is increased (i) prior to step (c) or (ii) after step (c) and maintained at high cell density during step (d).

2. The method according to claim 1, wherein the density of the cell culture grown to confluence is concentrated at least about 1.3 fold.

3. The method according to claim 1, wherein the cell density of the cell culture grown to confluence is between about 0.6×10^6 and about 7.0×10^6 cells/ml.

4. The method according to claim 1, wherein the microcarrier is selected from the group of microcarriers made of dextran, collagen, polystyrene, polyacrylamide, gelatine, glass, cellulose, polyethylene and plastic.

5. The method according to claim 1, wherein the microcarrier concentration in the culture of cells of step (a) is between about 0.5 g/l and about 14 g/l.

6. The method according to claim 1, wherein said cells are selected from the group of adherent cells of VERO, BHK, CHO, RK, RK44, RK13, MRC-5, MDCK, CEF or diploid monolayer cells.

EP0068274A1

7. The method according to claim 1, wherein said cells bound to a microcarrier are grown in serum free medium.

8. The method according to claim 1, wherein said cells bound to a microcarrier are grown in serum and protein free medium.

9. The method according to claim 1, wherein the virus is selected from the group of Influenza virus, Ross River Virus, Hepatitis A Virus, Vaccinia Virus and recombinant derivatives thereof, Herpes Simplex Virus, Japanese encephalitis Virus, West Nile Virus, Yellow Fever Virus and chimeric thereof, Rhinovirus and Reovirus.

10. The method according to claim 1, further comprising the step (e) harvesting the virus propagated.

11. A method for production of purified virus or virus antigen comprising the steps of (a) providing a culture of adherent cells bound to a microcarrier, (b) growing the cell culture to confluence, (c) infecting the culture of cells with a virus, (d) incubating said culture of cells infected with said virus to propagate said virus (e) harvesting the virus produced and (f) purifying said virus harvested, wherein the cell density of the biomass of the cell culture grown to confluence is increased (i) prior to step (c) or (ii) after step (c) and maintained at high cell density during step (d).

12. The method according to claim 11, wherein the virus produced is harvested from the cell culture supernatant.

13. The method according to claim 11, wherein the virus produced is harvested from the cell biomass.

Page 21 of 22

14. A method for production of Influenza virus, comprising the steps of (a) providing a culture of adherent cells bound to a microcarrier, (b) growing the cell culture to confluence, (c) infecting the cells with an Influenza virus and (d) incubating said culture of cells infected with said Influenza virus to propagate said virus, wherein the cell density of the biomass of the cell culture grown to confluence is increased (i) prior to step (c) or (ii) after step (c) and maintained at high cell density during step (d).

15. The method according to claim 14, wherein said cells are VERO cells.

16. The method according to claim 14, wherein said cells are MDCK cells.

17. The method according to claim 14, wherein said cells bound to a microcarrier are grown in serum free medium.

18. The method according to claim 14, wherein said cells bound to a microcarrier are grown in serum and protein free medium.

19. The method according to claim 14, wherein the cell culture grown to confluence is concentrated at least about 1.3 fold.

20. The method according to claim 14, wherein further comprising the step (e) of harvesting said Influenza virus or Influenza virus antigen produced.

21. The method according to claim 14, further comprising the step (f) of purifying said Influenza virus harvested.

22. A cell culture biomass of adherent cells bound to a microcarrier, wherein the biomass of cells in said cell culture is at least about 1.3 fold compared

Patent Application

to a cell culture that has been grown to confluence.

23. The culture according to claim 22, wherein said cells are VERO cells.

24. The culture according to claim 22, wherein said culture is serum free.

25. The culture according to claim 22, wherein said culture is serum and protein free.

26. The culture according to claim 22, wherein said cells are infected with a virus.

27. A cell culture biomass of VERO cells bound to a microcarrier, wherein the biomass of the VERO cells in said cell culture is at least about 1.3-fold compared to a VERO cell culture that has been grown to confluence.

28. The culture according to claim 27, wherein said culture is serum free.

29. The culture according to claim 27, wherein said culture is serum and protein free.

30. A cell culture biomass of adherent cells bound to a microcarrier infected with a virus, wherein the biomass of the infected cells in said cell culture is at least about 1.3-fold compared to a cell culture that has been grown to confluence prior to infection.

31. The culture according to claim 30, wherein said culture is serum free.

32. The culture according to claim 30, wherein said culture is serum and protein free.

33. The culture according to claim 30, wherein said cells are VERO cells.

34. A cell culture biomass of VERO cells bound to a microcarrier and cells infected with a virus, wherein the biomass of the VERO cells in said cell culture is at least about 1.3-fold compared to a VERO cell culture that has been grown to confluence.

35. A cell culture according to claim 34, infected with a virus selected from the group of Influenza virus, Ross River Virus, Hepatitis A Virus, Vaccinia Virus and recombinant derivatives thereof, Herpes Simplex Virus, Japanese encephalitis Virus, West Nile Virus, Yellow Fever Virus and chimeric thereof, Rhinovirus and Reovirus.

36. A cell culture biomass of VERO cells bound to a microcarrier and infected with a Influenza virus wherein the biomass of the VERO cells in said cell culture is at least about 1.3-fold compared to a VERO cell culture that has been grown to confluence.

37. A cell culture biomass of VERO cells bound to a microcarrier and infected with a Ross River Virus, wherein the biomass of the VERO cells in said cell culture is at least about 1.3-fold compared to a VERO cell culture that has been grown to confluence.

38. A cell culture biomass of VERO cells bound to a microcarrier and infected with a Vaccinia Virus, wherein the biomass of the VERO cells in said cell culture is at least about 1.3-fold compared to a VERO cell culture that has been grown to confluence.